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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 223-204-WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00538	International filing date *(day/month/year)* 13.08.2003	Priority date *(day/month/year)* 14.08.2002
International Patent Classification (IPC) or both national classification and IPC C07D453/02		
Applicant NEUROSEARCH A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.02.2004	15.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ousset, J-B Telephone No. +49 89 2399-8271

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00538

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-25 as originally filed

Claims, Numbers

1-35 received on 07.06.2004 with letter of 04.06.2004

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-4(all part),35

   because:

   ☒ the said international application, or the said claims Nos. 35 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-4 (all part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4(all part),5-34
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4(allpart),5-34
Industrial applicability (IA)	Yes:	Claims	1-4(all part),5-34
	No:	Claims	

2. Citations and explanations

   see separate sheet

SECTION III

1). Claim 35 relates to the treatment of human and/or animal bodies. According to Rule 67(1)(iv) an examination is not required for such claims.

SECTION V

1). The amendments filed with the Applicant's letter of 04.06.04 do not add any new subject-matter.

2). Relevant prior art is represented by:

D1: US-A-5 589 477 (CHOKAI SHOICHI ET AL) 31 December 1996 (1996-12-31)
D2: WO 98 15551 A (COURTEMANCHE GILLES ;BOVY PHILIPPE (FR); EVEN LUC (FR); SYNTHELABO) 16 April 1998 (1998-04-16)
D3: WO 99 31097 A (COURTEMANCHE GILLES ;SANOFI SYNTHELABO (FR); BOVY PHILIPPE R (FR);) 24 June 1999 (1999-06-24)
D4: US-A-5 998 404 (WARD JOHN S ET AL) 7 December 1999 (1999-12-07)
D5: US-A-5 646 289 (ALT CHARLES A ET AL) 8 July 1997 (1997-07-08)
D6: US-A-5 763 457 (BYMASTER FRANKLIN P ET AL) 9 June 1998 (1998-06-09)
D7: US-A-5 852 037 (BYMASTER FRANKLIN P ET AL) 22 December 1998 (1998-12-22)
D8: WO 98 27983 A (SAUERBERG PER ;NOVONORDISK AS (DK); HANSEN KRISTIAN TAGE (DK)) 2 July 1998 (1998-07-02)
D9: DATABASE STN INTERNATIONAL [Online] File ZCAPLUS, ZCAPLUS accession no. 1996:509522, Document no. 125:167796; YAMANOUCHI PHARMA CO LTD: 'Preparation of quinuclidine derivatives as squalene synthase inhibitors' XP002261104 & JP 08 134067 A 28 May 1996 (1996-05-28)

3). Due to the limitations carried out by the applicant, novelty is acknowledged vis-à-vis D1-D7. The group A cannot be either a pyrimidinyl moiety or an oxadiazolyl or an thiadiazolyl moiety.

4). D1 represents the closest prior art and differs from the content of the present application by the nature of the group A (pyrimidinyl group in D1).

Hence, the problem underlying the current application appears to be the provision of further polycyclic compounds useful for treating CNS disorders.

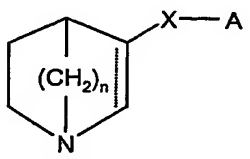
The data of the description (see page 25) show that this problem has been solved for the tested compounds and a reasonable generalisation thereof.

However, in view of the small structural difference between the compounds of D1 and those of the current application (more particularly when A is pyridazinyl), it is questionable whether the whole claimed scope leads to compounds retaining the claimed activity.
If the mere isomeric form of the group A (pyridazinyl versus pyrimidinyl) is to be regarded as not obvious for the skilled reader, it is not clear for which reasons, the same skilled person would regard the claimed generalisation as obvious alternatives of the tested compounds.
An inventive step on the whole claimed scope is not acknowledged.

5). For the assessment of the present claim 35 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS

1. A quinuclidine derivative represented by Formula I



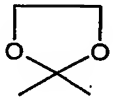
(I)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

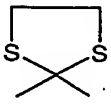
—— represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, -SO-, -SO_2-, -CH_2-, -S-CH_2-CH_2-, -CH_2-, -C(=CH_2)-,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and



; and

A represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl;

<u>provided, however,</u>

if X represents O or S;

then A is not phenyl or phenyl substituted with anything other than a phenyl group.

2. The quinuclidine derivative of claim 1, wherein ==== represents a single (covalent) bond.

3. The quinuclidine derivative of either one of claims 1-2, wherein n is 1, 2 or 3.

4. The quinuclidine derivative of any one of claims 1-3, wherein X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, and -CH_2-.

5. The quinuclidine derivative of any one of claims 1-4, wherein A represents a monocyclic or polycyclic carbocyclic group selected from

phenyl;

indanyl, in particular 4-indanyl and 5-indanyl;

indenyl, in particular 1-indenyl, 2-indenyl and 3-indenyl;

naphthyl, in particular 1-naphthyl and 2-naphthyl;

5,6,7,8-tetrahydro-naphthyl, in particular 5,6,7,8-tetrahydro-1-naphthyl and 5,6,7,8-tetrahydro-2-naphthyl;

azulenyl, in particular 1-azulenyl, 2-azulenyl and 3-azulenyl; and

fluorenyl, in particular 1-fluorenyl, 2-fluorenyl, 3-fluorenyl and 4-fluorenyl; and

anthracenyl, in particular 1-anthracenyl and 2-anthracenyl;

which carbocyclic group is optionally substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

6. The quinuclidine derivative of any one of claims 1-4, wherein A represents an aromatic monocyclic or polycyclic carbocyclic group selected from

phenyl;

indenyl, in particular 1-indenyl, 2-indenyl and 3-indenyl;

naphthyl, in particular 1-naphthyl and 2-naphthyl;

azulenyl, in particular 1-azulenyl, 2-azulenyl and 3-azulenyl; and

anthracenyl, in particular 1-anthracenyl and 2-anthracenyl;

which aromatic carbocyclic group is optionally substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

7. The quinuclidine derivative of claim 5, which is
(±)-3-(2-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(3-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(4-Phenylphenyloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(4-Phenylphenyl-methoxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(Naphthalen-2-yloxy)-1-aza-bicyclo[2.2.2]octane;
(±)-3-(5,6,7,8-Tetrahydro-2-naphthyloxy)-1-aza-bicyclo[2.2.2]octane; or
(±)-3-(5-Indanyloxy)-1-aza-bicyclo[2.2.2]octane;
or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

8. The quinuclidine derivative of any one of claims 1-4, wherein A represents a monocyclic or polycyclic heterocyclic group selected from
pyridyl, in particular pyrid-2-yl, pyrid-3-yl and pyrid-4-yl;
thienyl, in particular thien-2-yl and thien-3-yl;
furanyl, in particular furan-2-yl and furan-3-yl;
pyridazinyl, in particular pyridazin-3-yl and pyridazin-4-yl;
thiazolyl, in particular thiazol-2-yl, thiazol-4-yl and thiazol-5-yl;
thiadiazolyl, in particular 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl and 1,2,4-thiadiazol-5-yl;
quinolinyl, in particular quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl;
quinoxalinyl, in particular quinoxalin-2-yl and quinoxalin-3-yl;
benzimidazolyl, in particular benzimidazol-2-yl;
benzoxazolyl, in particular benzoxazol-2-yl;
benzthiazolyl, in particular benzthiazol-2-yl;
which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

9. The quinuclidine derivative of any one of claims 1-4, wherein A represents a monocyclic heterocyclic group selected from

pyridyl, in particular pyrid-2-yl, pyrid-3-yl and pyrid-4-yl;

thienyl, in particular thien-2-yl and thien-3-yl;

furanyl, in particular furan-2-yl and furan-3-yl;

pyridazinyl, in particular pyridazin-3-yl and pyridazin-4-yl;

thiazolyl, in particular thiazol-2-yl, thiazol-4-yl and thiazol-5-yl;

thiadiazolyl, in particular 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl and 1,2,4-thiadiazol-5-yl;

which monocyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl, which phenyl, 2-thienyl, 3-thienyl, 2-furanyl, 3-furanyl, and 3-pyridinyl groups may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

10. The quinuclidine derivative of claim 9, which is

(±)-3-(3,4,5-Trichloro-thien-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(5-Bromo-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(5-Phenyl-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-[5-(2,4-Difluoro-phenyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-[5-(3-Thienyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-[5-(2-Thienyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-[5-(3-Furanyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-[5-(3-Pyridyl)-thiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-(6-Chloro-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(6-Bromo-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(6-Phenyl-pyridazin-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-[6-(3-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-[6-(2-Thienyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-[6-(2-Furanyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-[6-(3-Furanyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-[6-(3-Pyridyl)-pyridazin-3-yloxy]-1-aza-bicyclo[2.2.2]octane;

(±)-3-(5-Phenyl-1,3,4-thiadiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(5-Phenyl-1,2,4-thiadiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane; or

(±)-3-[5-(2-Thienyl)-1,3,4-thiadiazol-2-yloxy]-1-aza-bicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

11. The quinuclidine derivative of any one of claims 1-4, wherein A represents a polycyclic heterocyclic group selected from

indolyl, in particular indol-2-yl and indol-3-yl;

isoindolyl, in particular isoindol-2-yl;

quinolinyl, in particular quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl;

quinoxalinyl, in particular quinoxalin-2-yl and quinoxalin-3-yl;

benzimidazolyl, in particular benzimidazol-2-yl;

benzoxazolyl, in particular benzoxazol-2-yl;

benzthiazolyl, in particular benzthiazol-2-yl;

benzisothiazolyl, in particular benzisothiazol-3-yl;

benztriazolyl, in particular 1,2,3-benztriazol-1-yl;

imidazo[1,2-b]pyridazinyl, in particular imidazo[1,2-b]pyridazin-6-yl;

dibenzofuranyl, in particular dibenzofuran-2-yl;

which monocyclic or polycyclic heterocyclic group is optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl, which phenyl group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

12. The quinuclidine derivative of claim 11, which is

(±)-3-[(1,3-Dione)-2-isoindolyl-methoxy]-1-azabicyclo[2.2.2]octane;

(±)-3-[(1,3-Dione)-2-isoindolyl-ethoxy]-1-azabicyclo[2.2.2]octane;

(±)-3-(2-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(2-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane methylium iodide;

(±)-3-(6-Quinolinyloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(2-Quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(2-Quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane methylium iodide;

(±)-3-(3-Chloro-2-quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(3-Methoxy-2-quinoxalinyloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(Benzoxazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(Benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(6-Chloro-benzothiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(1,2-Benzoisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

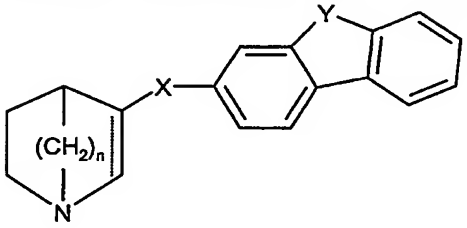
(±)-3-(1,2-Benzoisothiazol-3-yloxy)-1-aza-bicyclo[2.2.2]octane;

(±)-3-(1-Methyl-benzoimidazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane; or

(±)-3-(Benzotriazol-1-yloxy)-1-azabicyclo[2.2.2]octane;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

13. The quinuclidine derivative of claim 1, represented by Formula II



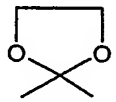
(II)

wherein

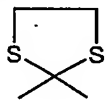
——— represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, -SO-, -SO_2-, -CH_2-, -S-CH_2-CH_2-, -CH_2-, -C(=CH_2)-,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,



, and



; and

Y represents O, S, SO_2, or NR', wherein R' represents hydrogen or alkyl.

14. The quinuclidine derivative of claim 13, wherein ——— represents a single (covalent) bond.

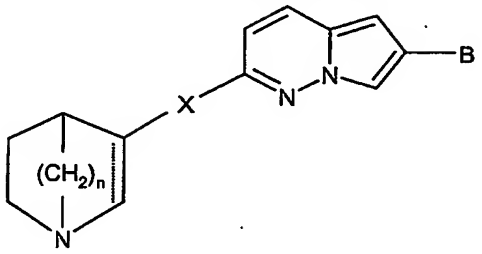
15. The quinuclidine derivative of either one of claims 13-14, wherein n is 1, 2 or 3.

16. The quinuclidine derivative of any one of claims 13-15, wherein X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, and -CH_2-.

17. The quinuclidine derivative of any one of claims 13-15, wherein Y represents O, S, SO_2, or NR', wherein R' represents hydrogen or alkyl.

18. The quinuclidine derivative of claim 13, which is
(±)-3-(Dibenzofuran-2-yloxy)-1-azabicyclo[2.2.2]octane;
or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

19. The quinuclidine derivative of claim 1, represented by Formula III



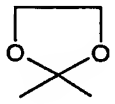
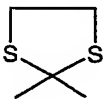
(III)

wherein

==== represents an optional double bond;

n is 1, 2 or 3;

X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, -SO-, -SO_2-, -CH_2-, -S-CH_2-CH_2-, -CH_2-, -C(=CH_2)-,-NH-, -N(alkyl)-, -C(=O)-, -C(=S)-,

 , and  ; and

B represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

20. The quinuclidine derivative of claim 19, wherein ---- represents a single (covalent) bond.

21. The quinuclidine derivative of either one of claims 19-20, wherein n is 1, 2 or 3.

22. The quinuclidine derivative of any one of claims 19-21, wherein X represents a linker selected from -O-, -O-CH_2-, -O-CH_2-CH_2-, -S-, and -CH_2-.

23. The quinuclidine derivative of any one of claims 19-22, wherein B represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3, CN, NO_2, NH_2, carboxy, carbamoyl, amido, sulfamoyl, and phenyl.

24. The quinuclidine derivative of claim 23, wherein B represents a phenyl group, which phenyl is optionally substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, alkoxy, cycloalkoxy, halo, CF_3, CN, NO_2, NH_2, and phenyl.

25. The quinuclidine derivative of claim 24, which is
(±)-3-(2-Phenyl-imidazo[1,2-b]pyridazin-6-yloxy)-1-azabicyclo[2.2.2]octane;
or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

26. A pharmaceutical composition comprising a therapeutically effective amount of a quinuclidine derivative of any one of claims 1-25, or a pharmaceutically-acceptable addition salt thereof.

27. Use of a quinuclidine derivative of any one of claims 1-25, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors.

28. The use according to claim 27, wherein the disease, disorder or condition relates to the central nervous system.

29. The use according to claim 28, wherein the disease, disorder or condition is anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

30. The use according to claim 27, wherein the disease, disorder or condition are associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

31. The use according to claim 27, wherein the disease, disorder or condition is related to the endocrine system, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

32. The use according to claim 27, wherein the disease, disorder or condition is a neurodegenerative disorders, including transient anoxia and induced neuro-degeneration.

33. The use according to claim 27, wherein the disease, disorder or condition is an inflammatory disorder, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

34. The use according to claim 27, wherein the disease, disorder or condition is mild, moderate or even severe pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

35. The use according to claim 27, wherein the disease, disorder or condition is associated with withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

36. A method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a quinuclidine derivative of any one of claims 1-25.